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PATENT
Attorney Docket No.: A-58634-7/RFT/RMS/RMK

In re application of:

MEADE, *et al.*

Serial No. 09/866,512

Filed: May 24, 2001

For: MAGNETIC RESONANCE IMAGING AGENTS FOR THE DETECTION OF PHYSIOLOGICAL AGENTS

Examiner: Not Yet Assigned

Group Art Unit: Not Yet Assigned

CERTIFICATE OF MAILING

I hereby certify that this correspondence, including listed enclosures, is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on

Dated: March 4, 2002

Signed: Mary McFarland
Mary McFarland

PRELIMINARY AMENDMENT

COPY OF PAPERS ORIGINALLY FILED

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

This Preliminary Amendment is being submitted in reply to the Notice to File Missing Parts of Nonprovisional Application dated August 9, 2001. This Amendment is accompanied by a petition for a five month extension of time and the appropriate fees, making this a timely response. The present Amendment is submitted to comply with requirements for patent applications containing nucleotide sequence and /or amino acid sequences and to submit new claims. The Commissioner is authorized to charge any fees, including extension fees, which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-58634-7/RFT/RMS/RMK).

Please amend the application as follows and to comply with requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures in adherence with rules 37 C.F.R. § 1.821-1.825:

In the Specification

Please replace the paragraph starting on page 18, line 26, with the following rewritten paragraph:

– Preferred target substance/peptide blocking moiety pairs include, but are not limited to, cat B and GGGF (SEQ ID NO: 1); cat B and GFQGVQFAGF (SEQ ID NO: 2); cat B and GFGSVGFAGF (SEQ ID NO: 3); cat B and GLVGGAGAGF (SEQ ID NO: 4); cat B and GGFLGLGAGF (SEQ ID NO: 5); cat D and GFGSTFFAGF (SEQ ID NO: 6); caspase-3 and DEVD (SEQ ID NO: 7); MMP-7 and PELR (SEQ ID NO: 8); MMP-7 and PLGLAR (SEQ ID NO: 9); MMP-7 and PGLWA-(D-arg) (SEQ ID NO: 10); MMP-7 and PMALWMR (SEQ ID NO: 11); and MMP-7 and PMGLRA (SEQ ID NO: 12).–

Please replace the paragraph starting on page 40, line 3, with the following rewritten paragraph:

–In a preferred embodiment, the targeting moiety is a nuclear localization signal (NLS). NLSs are generally short, positively charged (basic) domains that serve to direct the moiety to which they are attached to the cell's nucleus. Numerous NLS amino acid sequences have been reported including single basic NLS's such as that of the SV40 (monkey virus) large T Antigen (Pro Lys Lys Lys Arg Lys Val, SEQ ID NO: 13), Kalderon (1984), et al., Cell, 39:499-509; the human retinoic acid receptor-ß nuclear localization signal (ARRRRP, SEQ ID NO: 14); NFκB p50 (EEVQRKRQKL, SEQ ID NO: 15; Ghosh et al., Cell 62:1019 (1990); NFκB p65 (EEKRKRTYE, SEQ ID NO: 16; Nolan et al., Cell 64:961 (1991); and others (see for example Boulikas, J. Cell. Biochem. 55(1):32-58 (1994), hereby incorporated by reference) and double basic NLS's exemplified by that of the Xenopus (African clawed toad) protein, nucleoplasmin (Ala Val Lys Arg Pro Ala Ala Thr Lys Lys Ala Gly Gln Ala Lys Lys Lys Lys Leu Asp, SEQ ID NO: 17), Dingwall, et al., Cell, 30:449-458, 1982 and Dingwall, et al., J. Cell Biol., 107:641-849; 1988). Numerous localization studies have demonstrated that NLSs incorporated in synthetic peptides or grafted onto reporter proteins not normally targeted to the cell nucleus cause these peptides and reporter proteins to be concentrated in the nucleus. See, for example, Dingwall, and Laskey, Ann, Rev. Cell Biol., 2:367-390, 1986; Bonnerot, et al., Proc. Natl. Acad. Sci. USA, 84:6795-6799, 1987; Galileo, et al., Proc. Natl. Acad. Sci. USA, 87:458-462, 1990.–

On page 53, immediately preceding the claims, insert the enclosed text entitled "SEQUENCE LISTING".

In the Claims

Please cancel claims 1-11 without prejudice or disclaimer.

Please add the following new claims:

–12. A composition comprising:

a) a polymer;

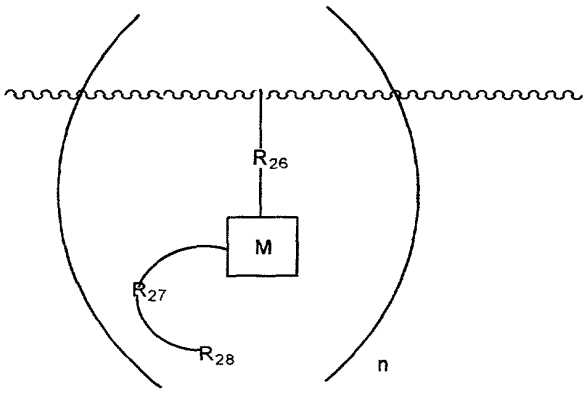
b) at least one MRI agent comprising:

i) at least one chelator comprising a paramagnetic metal ion; and,

ii) a blocking moiety covalently attached to said chelator which hinders the rapid exchange of water in the remaining coordination sites, wherein said blocking moiety will interact with a target substance such that the exchange of water in the remaining coordination sites is increased; and

c) a linker group attaching said MRI agent to said polymer.

13. An MRI agent according to claim 1 having the formula comprising:



wherein

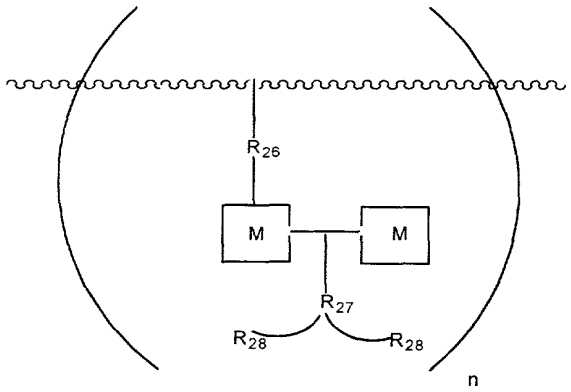
M is a chelator comprising a paramagnetic metal ion;

R_{26} and R_{27} are linker groups;

R_{28} is a blocking moiety; and,

n is an integer.

14. An MRI agent according to claim 1 having the formula comprising:



wherein

M is a chelator comprising a paramagnetic metal ion;

R_{26} and R_{27} are linker groups;

R_{28} is a blocking moiety; and

n is an integer.

15. An MRI agent according to claims 1, 2, or 3 wherein said paramagnetic metal ion is selected from the group comprising gadolinium III (Gd+3 or Gd(III)), iron III (Fe+3 or FE(III)), manganese II (Mn+2 or Mn(II)), dysprosium (Dy+3 or Dy(III)), or chromium (Cr+3 or Cr(III).

16. An MRI agent according to claim 15 where said paramagnetic ion is Gd(III).

17. An MRI agent according to claims 1, 2 or 3 wherein said linker groups are alkyl groups.

18. An MRI agent according to claim 17 wherein said alkyl groups are substituted alkyl groups.

19. An MRI agent according to claims 1, 2 or 3 wherein said linker groups are aryl groups.

20. An MRI agent according to claims 19 wherein said aryl groups are substituted aryl groups.

21. An MRI agent according to claims 1, 2 or 3 wherein at least one of said linker groups are selected from the group comprising p-aminobenzyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, propionic acid, aminobutyl, p-alkyl phenols, and 4-alkylimidazaole.

22. An MRI agent according to claims 1, 2 or 3 wherein said blocking moiety is a peptide.

23. An MRI agent according to claim 22 wherein said peptide binds to an metalloproteinase.

24. An MRI agent according to claim 23 wherein said peptide is selected from the group comprising PELR (SEQ ID NO: 8), PLGLAR (SEQ ID NO: 9), PGLWA-(D-arg) (SEQ ID NO: 10), PMALWMR (SEQ ID NO: 11), and PMGLRA (SEQ ID NO:12).

25. An MRI agent according to claims 1, 2 or 3 wherein said polymer is selected from the

group comprising functionalized dextrans, styrene polymers, polyethylene, polyanions and polycations.

26. An MRI agent according to claim 25 wherein said polycation is polylysine.

27. An MRI agent according to claim 1, 2, or 3 wherein said polymer comprises a plurality of said MRI agents.

28. A method of magnetic resonance imaging of a cell, tissue or patient comprising administering an MRI agent according to claim 1, 2, or 3 to a cell, tissue or patient and rendering a magnetic resonance image of said cell, tissue or patient.

REMARKS

Claims 1-11 have been cancelled without prejudice or disclaimer. Claims 12-28 are newly added. Support for new claims 12-14 is found in Figures 10H and I, and in the specification at page 6, line 28 through page 7, line 10, and at page 33, line 12 through page 34, line 29. Support for new claims 15 and 16 is found in the specification at page 10, lines 15-22. Support for new claims 17-21 is found in the specification at page 23, lines 6-26. Support for new claims 22-24 is found in the specification at 18, lines 4-29. Support for new claims 25-27 is found at page 33, line 12 through page 34, line 29. Support for new claim 28 is found in original claim 11.

These amendments are made in adherence with 37 C.F.R. § 1.821-1.825. This amendment is accompanied by a floppy disc containing the above named sequence,

SEQUENCE ID NUMBERS 1-17, in computer readable form, and a paper copy of the sequence information. The computer readable sequence listing was prepared through use of the software program "Patent-In" provided by the PTO. The information contained in the computer readable disk is identical to that of the paper copy. This amendment contains no new matter. Applicant submits that this amendment, the accompanying computer readable sequence listing, and the paper copy thereof serve to place this application in a condition of adherence to the rules 37 C.F.R. § 1.821-1.825.

Attached hereto is a marked-up version of the changes made to the specification by the current amendments. The attached page is captioned "Version with markings to show changes made."

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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Robin M. Silva, Reg. No. 38,304

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph starting on page 18, line 26, has been amended as follows:

– Preferred target substance/peptide blocking moiety pairs include, but are not limited to, cat B and GGGF (SEQ ID NO: 1); cat B and GFQGVQFAGF (SEQ ID NO: 2); cat B and GFGSVGFAGF (SEQ ID NO: 3); cat B and GLVGGAGAGF (SEQ ID NO: 4); cat B and GGFLGLGAGF (SEQ ID NO: 5); cat D and GFGSTFFAGF (SEQ ID NO: 6); caspase-3 and DEVD (SEQ ID NO: 7); MMP-7 and PELR (SEQ ID NO: 8); MMP-7 and PLGLAR (SEQ ID NO: 9); MMP-7 and PGLWA-(D-arg) (SEQ ID NO: 10); MMP-7 and PMALWMR (SEQ ID NO: 11); and MMP-7 and PMGLRA (SEQ ID NO: 12). –

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